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DRINKING WATER CRITERIA DOCUMENT FOR NICKEL

Prepared for

OFFICE OF DRINKING WATER

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The Office of Drinking Water (ODW), U.S. Environmental Protection Agency has prepared a Drinking Water Criteria Document on nickel. This Criteria Document is an extensive review of the following topics:

- Physical and chemical properties of nickel
- Toxicokinetics and human exposure to nickel
- Health Effects of nickel in humans and animals
- Mechanisms of toxicity of nickel
- Quantification of toxicological effects of nickel

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LIST OF ABBREVIATIONS

AADI	Adjusted acceptable daily intake
ADI	Acceptable daily intake
bw	Body weight
GI	Gastrointestinal
HA	Health advisory
IARC	International Agency for Research on Cancer
i.m.	Intramuscular
i.p.	Intraperitoneal
LD_{50}	Concentration lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
TWA	Time-weighted average

IV. HUMAN EXPOSURE

Humans may be exposed to chemicals such as nickel from a variety of sources, including drinking water, food, ambient air, occupational settings and consumer products. This analysis of human exposure to nickel is limited to drinking water, food and ambient air because those media are considered to be sources common to all individuals. Even in limiting the analysis to these three sources, it must be recognized that individual exposure will vary widely based on many personal choices and on several factors over which there is little control. Where one lives, works and travels, what one eats, and physiologic characteristics related to age, sex and health status can all profoundly affect daily exposure and intake. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

In the Exposure Estimation Section of this chapter, available information is presented on the range of human exposure and intake for nickel from drinking water, food and ambient air for the 70 kg adult male. It is not possible to provide an estimate of the number of individuals experiencing specific combined exposures from those three sources. However, the Summary Section of this chapter provides some insight into the relative contributions of the three sources, especially drinking water, to the range of intake values suggested by the available data.

Exposure Estimation

Drinking Water. Limited information was obtained on the occurrence of nickel in drinking water. Only one of the Federal surveys [the 1969 Community Water Supply Survey (CWSS)] included nickel as an analyte. Several

additional studies on nickel in drinking water samples were reported in Ciccone and Associates (1984). However, the detection limits for the reported studies were usually not given.

The CWSS (McCabe et al., 1970) examined 120 surface water supplies, 613 groundwater supplies, 152 supplies with mixed water or purchased sources, and 84 special systems (trailer parks, tourist and other institutions) in the United States in 1969. Samples were analyzed for various chemicals including nickel. A total of 2595 distribution samples were collected. Although McCabe et al. (1970) reported that levels of nickel were analyzed for in the CWSS samples, the report does not present data on the levels of nickel found in the samples. However, a personal communication with McCabe (NAS, 1975) revealed that nickel concentrations in the CWSS samples ranged from 1-75 µg/ℓ, with a mean value of 4.8 µg/ℓ and a 78% frequency of detection. Only 0.5% of the samples contained >25 µg/ℓ of nickel.

Greathouse and Craun (1978) studied the occurrence of inorganics in household drinking water. A total of 3834 drinking water samples were randomly collected nationwide. Nickel was detected in 83% of the samples taken. An overall mean concentration of 2.0 µg/ℓ was reported. The detection limit for nickel in this study was 0.1 µg/ℓ.

Public urban water supplies of the 100 largest cities in the U.S. (according to the 1960 U.S. census) were studied by Durfor and Becker (1962). The total number of samples analyzed was not reported and the water sources varied. Nickel was detected in 93% of the samples with a median value of <2.7 µg/ℓ, and a range of not detected to 34 µg/ℓ.

In a study of trace elements in water, Kopp (1969) analyzed random grab samples of finished water collected nationwide from surface water systems. Nickel occurred in 4.6% of the 380 samples taken. A mean of 34.2 µg/ℓ and a range of 1-490 µg/ℓ was reported, although only positive samples were used to calculate the mean.

Two corrosion-related studies were also reported in Ciccone and Associates (1984). In a study of trace metals in drinking water in the Boston metropolitan area (Boston, Cambridge and Somerville), Karalekas et al. (1976) analyzed finished and distribution water samples from 383 surface water sources. A total of 936 samples were taken, with one standing and one running sample taken from each distribution source. The authors reported that detectable levels of nickel were not found in either the finished or distribution water samples. The detection limit was 10 µg/ℓ.

In a Seattle, Washington water metals survey, Courchene et al. (1978) analyzed a total of 148 distribution water samples representative of the total water supply for Seattle; water was obtained from the Cedar and Tolt rivers. Sixty-nine supplies were sampled after 5-8 hours stagnation time (standing samples), and 79 supplies were sampled after the systems were flushed for 5 minutes (running samples). Nickel was found in 26.6% of the Cedar river standing samples and 7.6% of the Cedar River running samples, with mean concentrations of 7.0 µg/ℓ (range of 0.0-43.0 µg/ℓ) and 2.0 µg/ℓ (range of 0.0-28.0 µg/ℓ), respectively. The mean concentration for Tolt river standing samples was 1.0 µg/ℓ (range of 0.0-<8.0 µg/ℓ), with no frequency of occurrence reported. Nickel was not detected in any Tolt river running sample. Although some values are reported as low as 1.0 µg/ℓ, the detection limit was reported as 5.0 µg/ℓ.

The levels of nickel and the frequency with which it is observed varies greatly in the studies obtained. Assuming that nickel is present at the highest concentration reported, i.e., 490 µg/ℓ in the Kopp study, the daily intake for the 70 kg adult male consuming 2 ℓ/day of drinking water would be 980 µg/day or 14 µg/kg/day.

Diet. According to NAS (1975), human exposure to nickel in food derives from the natural occurrence of nickel in food ingredients and from manmade sources, such as alloys, food-processing equipment and fungicides, which may increase the amount of nickel in food substances beyond the levels that are naturally present.

Schroeder et al. (1961) reported concentrations of nickel in condiments, seafood, meats, grains, vegetables and fluids. They noted that most whole grains appeared to contain considerable amounts of nickel; the largest quantities of nickel were detected in buckwheat (6450 µg/kg), rye (2700 µg/kg), oats (2600 µg/kg), corn (700 µg/kg), rice (1800 µg/kg) and wheat (750 µg/kg). Fairly large amounts of nickel were detected in legumes (170-2590 µg/kg), tea (7600 µg/kg) and cocoa (5000 µg/kg). All American vegetables sampled contained some concentrations of nickel, and two of four fruits were relatively deficient in nickel. Schroeder et al. (1961) noted the low levels of nickel in eggs (30 µg/kg) and milk (30 µg/kg).

The levels of nickel ingested from foods may vary widely depending upon the types of foods consumed and their method of preparation. For example, according to Schroeder et al. (1961), a person who ingests a 2300-calorie

diet containing 100 g of protein, 250 g of carbohydrate and 100 g of fat and who consumes meat, milk, fruit, refined white bread, wheatena, butter and corn oil would ingest 3-10 μg/kg of nickel However, a diet that has the same caloric value and the same proportions of protein, carbohydrate and fat might contain 700-900 μg/kg of nickel, if the person consumes oysters, meat, milk, eggs, oats, whole-wheat or rye bread, some vegetables, potatoes and legumes, with little added fat. In addition, the wide range of dietary intake of nickel may result from variable ingestion of beverages -- such as tea, coffee, beer and red wine -- that contain more than 1000 μg/kg of nickel (Schlettwein-Gsell and Mommsen-Straub, 1971). Metal cooking pots and eating utensils that are made of nickel-containing alloys can also contribute to the dietary ingestion of nickel (Titus et al., 1930).

Table IV-1 summarizes reported dietary intakes of nickel by humans. The daily intake averages range from 165-500 μg/day: the intake values range from 107-696 μg/day.

Air. Very limited information was obtained on the presence of nickel in ambient air. The U.S. EPA's Environmental Monitoring Systems Laboratory provided information from a nationwide study on nickel concentrations in ambient air. The data obtained from this study includes samples that were collected and analyzed from 424 sites in 48 states, the District of Columbia, Puerto Rico and the Virgin Islands for the years 1977-1983 (U.S. EPA, 1984). Out of a total of 23,782 samples, concentrations of nickel in the air samples ranged from 0.006-0.917 μg/m^3, with a range of mean and median values by city and by year of 0.0028-0.1885 μg/m^3 and 0.006-0.130 μg/m^3, respectively.

TABLE IV-1

Estimated Dietary Intake of Nickel by Humans*

Average Intake (µg/day)	Range (µg/day)	Reference
NC	300-600	Schroeder et al., 1961
300	---	Taktakishvili, 1963
NC	170-330	Tipton et al., 1969
500	---	Louria et al., 1972
NC	280-310	Nodiya, 1972
451	288-696	Murthy et al., 1973
165	107-221	Myron et al., 1978

*Source: NAS, 1980

NC = Not calculated

Summary

Table IV-2 presents a general view of the total amount of nickel received by a 70 kg adult male from ambient air, food and drinking water. Five separate exposure levels in drinking water, three separate exposure levels in food and one exposure level from ambient air are shown in the table.

The data presented have been selected from an infinite number of possible combinations of concentrations for the three sources. Whether exposure occurs at any specific combination of levels is not known; nor is it possible to determine the number of persons that would be exposed to nickel at any of the combined exposure levels. The data presented represent possible exposures based on the occurrence data and the estimated intakes.

The drinking water levels selected are representative of the range of levels observed in the studies obtained. It is assumed that the 70 kg adult male consumes 2 ℓ/day of drinking water.

The dietary nickel intake levels selected are similarly representative of the range of levels that were obtained in the National Academy of Sciences study (see Table IV-1 in Diet Section).

The ambient air intake level was determined by using the high value of the range of median levels reported in ambient air (see Air Section). There was essentially no difference in the contribution of ambient air to total exposure from nickel by calculating total intake using the low value of the range of median levels. It is assumed here that the average adult male

TABLE IV-2

Estimated Intake of Nickel from the Environment by Adult Males
in µg/kg/day

Concentration in Drinking Water (µg/ℓ)	Estimated Total Intake in µg/kg/day (% from drinking water) Based on Food Levels of:		
	Low (150 µg/day)	Intermediate (350 µg/day)	High (500 µg/day)
0.0	2.1 (0%)	5.0 (0%)	7.1 (0%)
1.0	2.2 (1%)	5.1 (0.6%)	7.2 (0.4%)
5.0	2.3 (6%)	5.2 (3%)	7.3 (2%)
50	3.5 (40%)	6.4 (22%)	8.5 (16%)
500	16 (87%)	19 (74%)	21 (66%)

Intake from each source:

Water: 1.0 µg/ℓ: 0.029 µg/kg/day
5.0 µg/ℓ: 0.14 µg/kg/day
50 µg/ℓ: 1.4 µg/kg/day
500 µg/ℓ: 14 µg/kg/day

Food: 150 µg/day: 2.1 µg/kg/day
350 µg/day: 5.0 µg/kg/day
500 µg/day: 7.1 µg/kg/day

Air: 0.13 µg/m³: 0.043 µg/kg/day

inhales 23 m^3 of air per day (ICRP, 1975). Assuming an intake of 0.043 µg/kg/day from air and a food intake range of 150-500 µg/day, drinking water would be the predominant source of nickel exposure in the adult male when drinking water levels exceed ~75-250 µg/ℓ.

An accurate assessment of the number of individuals for which drinking water is the predominant source of exposure cannot be determined from the data since specific locations containing high concentrations of nickel in drinking water and low concentrations of nickel in ambient air and food are unknown.

The relative source contribution data are based on estimated intake and do not account for a possible differential absorption rate for nickel by route of exposure. In addition, the effects of the chemical on the body may vary by different routes of exposure.

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VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

The quantification of toxicological effects of a chemical consists of an assessment of the noncarcinogenic and carcinogenic effects. In the quantification of noncarcinogenic effects, an ADI is calculated. AADI and HA values for the chemical are then calculated to define the appropriate drinking water concentrations to limit human exposure. For ingestion data, this approach is illustrated as follows:

$$\text{ADI} = \frac{\text{(NOAEL or LOAEL in mg/kg/day) (body weight in kg)}}{\text{uncertainty/safety factor}} = \text{mg/day}$$

$$\text{AADI} = \frac{\text{ADI}}{\text{drinking water volume in } \ell\text{/day}} = \text{mg/}\ell$$

where:

NOAEL = no-observed-adverse-effect level
LOAEL = lowest-observed-adverse-effect level
Body weight = 70 kg for adult or 10 kg for child
Drinking water volume = 2 ℓ/day for adults or 1 ℓ/day for children
Uncertainty/safety factor = 10, 100 or 1,000.

Utilizing these questions, the following drinking water concentrations are developed for noncarcinogenic effects:

1. A 1-day HA for 10 kg child
2. A 1-day HA for 70 kg adult
3. A 10-day HA for 10 kg child
4. A 10-day HA for 70 kg adult
5. A lifetime AADI for a 70 kg adult.

The distinctions made between the HA calculations (items 1 through 4) are associated with the duration of anticipated exposure. Items 1 and 2 assume a single acute exposure to the chemical. Items 3 and 4 assume a limited period of exposure (possibly 1 to 2 weeks). The HA values will not be used in establishing a drinking water standard for the chemical. Rather, they will be used as informal scientific guidance to municipalities and other organizations when emergency spills or contamination situations occur. The AADI value (item 5) is intended to provide the scientific basis for establishing a drinking water standard based upon noncarcinogenic effects.

A NOAEL or LOAEL is determined from animal toxicity data or human effects data. For animal data, this level is divided by an uncertainty factor because there is no universally acceptable quantitative method to extrapolate from animals to humans. The possibility must be considered that humans are more sensitive to the toxic effects of chemicals than are animals. For human data, an uncertainty factor is also used to account for the heterogeneity of the human population in which persons exhibit differing sensitivity to toxic chemicals. An Office of Drinking Water (ODW) modification of the guidelines set forth by the National Academy of Sciences (NAS, 1977, 1980) is typically used in establishing uncertainty factors as follows:

- An uncertainty factor of 10 is used when good acute or chronic human exposure data are available and supported by acute or chronic toxicity data in other species.
- An uncertainty factor of 100 is used when good acute or chronic toxicity data identifying NOEL/NOAEL are available for one or more species, but human data are not available.

- An uncertainty factor of 1000 is used when limited or incomplete acute or chronic toxicity data are available or when only the acute or chronic toxicity data that identify a LOAEL (but not NOEL/NOAEL) for one or more species are available.

The uncertainty factor used for a specific risk assessment is judgmental. Factors that cannot be incorporated in the NAS/ODW guidelines for selection of an uncertainty factor, but must be considered include the following: (1) the quality of the toxicology data, (2) the significance of the adverse effect and (3) the existence of counterbalancing beneficial effects.

If toxicological evidence requires the chemical to be classified as a potential carcinogen (however, there is insufficient evidence to classify nickel as a carcinogen following oral exposure), mathematical models are used to calculate the estimated excess cancer risks associated with the ingestion of the chemical by drinking water. The bioassay data used in these estimates are from animal experiments. In order to predict the risk for humans, these data must be converted to an equivalent human dose. This conversion includes correction for noncontinuous animal feeding, nonlifetime studies and for the difference in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average human body weight is 70 kg and that the average human consumes 2 ℓ of water/day. The multistage model is then fit to the equivalent human data to estimate the risk at low doses. The upper 95% confidence limit of this estimate is used. Excess cancer risks can also be estimated using other models such as the one-hit model, the Weibull model, the logit model and the profit model. There is no basis,

in the current understanding of the biological mechanisms involved in cancer, to choose among these models. The estimates of low doses for these models can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of risk rate levels has an inherent uncertainty. This is because the tools of scientific measurement, by their very nature, involve both systematic and random error. In most cases, only studies using experimental animals have been performed. There is thus uncertainty when the data are extrapolated to humans. When developing risk rate levels, several other areas of uncertainty exist, such as (1) incomplete knowledge concerning the health effects of contaminants in drinking water, (2) the impact of test animal age, sex and species and the nature of target organ systems examined in the toxicity study results and (3) the actual rate of exposure of internal targets in test animals or humans. Dose-response data are usually only available for high levels of exposure, not for the lower levels of exposure for which a standard is being set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

Noncarcinogenic Effects

Pharmacokinetic data indicate that the absorption of dietary nickel from the GI tract of laboratory animals is low, ranging from 1-10% (Horak and Sunderman, 1973; Nodiya, 1972; Nomoto and Sunderman, 1970; Perry and Perry, 1959; Tedeschi and Sunderman, 1957). The extent of absorption is apparently similar whether nickel is found in aqueous solution or in the diet. Ho and Furst (1973) found that urinary excretion of ^{63}Ni administered orally to

rats as nickel chloride in dilute acid solution was 3-6% with the remainder found in the feces. These percentages fall within the range observed for dietary nickel.

Short-Term Exposure. As expected from the low GI absorption, toxicity of nickel is much lower by the oral route than by parenteral routes. The LD_{50} values for oral and parenteral routes are summarized in Table VIII-1. Oral LD_{50} values converted to mg nickel/kg bw ranged from 105 mg/kg bw for nickel chloride in male rats (Itskova et al., 1969) to 186 mg/kg bw for nickelocene in mice (Haro et al., 1968). In the excretion study by Ho and Furst (1973) no overt toxic effects were observed in anesthetized rats given a dose of up to 64 mg nickel/kg bw. No other information on the acute toxicity of nickel following oral exposure was located in the available literature.

Oral subchronic and chronic toxicity and teratogenicity studies in laboratory animals are summarized briefly in Table VIII-2. Whanger (1973) added nickel acetate to the diet of weanling OSU brown rats (35 days old, 24/group) for 6 weeks at concentrations of 100, 500 or 1000 ppm nickel. Assuming young rats consume the equivalent of 10% of their bw/day, for a 6-week study the daily intake of nickel can be estimated as 10, 50 or 100 mg/kg bw. Body weight gain during the 6 weeks of treatment was significantly reduced at 500 ppm and rats lost weight at 1000 ppm (100 mg Ni/kg bw). Food consumption was not reported. At 500 ppm (50 mg Ni/kg bw) and 1000 ppm (100 mg Ni/kg bw) a dose-related decrease in hemoglobin concentration in blood, packed cell volume and plasma alkaline phosphatase activity was observed. Plasma ceruloplasmin concentrations were not significantly

TABLE VIII-1

Oral and Parenteral LD_{50} Values for Nickel

Route	Compound	Species/ Strain	Sex	Reported LD (mg/kg bw)	Nickel[a] LD (mg NI/kg bw)	Reference
Oral	nickel acetate	rats/F-344	F	350	116	Haro et al., 1968
Oral	nickel acetate	rats/F-344	M	360	120	Haro et al., 1968
Oral	nickel acetate	mice/Swiss	F	420	139	Haro et al., 1968
Oral	nickel acetate	mice/Swiss	M	410	136	Haro et al., 1968
Oral	nickelocene	rats/F-344	F	500	156	Haro et al., 1968
Oral	nickelocene	rats/F-344	M	490	152	Haro et al., 1968
Oral	nickelocene	mice/Swiss	M, F	600	186	Haro et al., 1968
Oral	nickel chloride	rats[b]	F	285	129	Itskova et al., 1969
Oral	nickel chloride	rats[b]	M	232	105	Itskova et al., 1969
i.p.	nickel acetate	rats/F-344	M, F	23	8	Haro et al., 1968
i.p.	nickel acetate	mice/Swiss	M, F	32	11	Haro et al., 1968
i.p.	nickelocene	rats/F-344	M, F	50	16	Haro et al., 1968
i.p.	nickelocene	mice/Swiss	M, F	86	27	Haro et al., 1968
i.p.	nickel chloride	rats/F-344	F	14	6	Horak et al., 1976
i.m.	nickel chloride	rats/F-344	F	51	23	Horak et al., 1976

[a]Converted dose from nickel compound to nickel

[b]The strain was not reported in the available reviews of this Russian study.

TABLE VIII-2

Summary of Oral Toxicity and Fetotoxicity of Nickel in Laboratory Animals

Duration	Species/ Strain	Sex/No.	Vehicle	Compound	Dose	Converted[a] Dose (mg Ni/kg bw)	Effects	Reference
6 weeks	rats/OSU	24 weanlings/NR	diet	nickel acetate	100, 500, 1000 ppm Ni	10, 50, 100	No effects at lowest dose (100 ppm). At 500 and 1000 ppm: body weight gain depressed, alterations in hematology parameters, cytochrome oxidase activity and iron content of organs.	Whanger, 1973
4 months	rats/NR	10 male/ group	drinking water	nickel chloride	225 ppm Ni	17.6	Significantly lower body weight and serum lipid and cholesterol concentration at sacrifice.	Clary, 1975
2 years	beagle dogs	3/sex/group	diet	nickel sulfate hexahydrate	0, 100, 1000 2500 ppm Ni	0, 3, 29, 70	No significant effects at 100 or 1000 ppm. Depressed body weight gain, altered organ-to-body weight ratios and histopathological effects in the lungs at the highest dose (2500 ppm).	Ambrose et al., 1976
2 years	rats/Wistar-derived	25/sex/ group	diet	nickel sulfate hexahydrate	0, 100, 1000, 2500 ppm Ni	0, 5, 50, 125	No significant effects at lowest doses. Depressed body weight gain, altered organ-to-body weight ratios at 1000 and 2500 ppm. No effect on hematology, histopathology.	Ambrose et al., 1976
Lifetime	rats/Long-Evans BLU(LE)	52/sex/ group	drinking water	NR	0, 5 ppm Ni	0.02, 0.41[b]	Body weight in 5 ppm group tended to be higher initially, but was significantly lower at 18 months. No clear adverse effects.	Schroeder et al., 1974
3 generation	rats/Wistar-derived	20 females	diet	nickel sulfate hexahydrate	0, 250, 500, 1000 ppm Ni	0, 12.5, 25, 50	Reproductive study. Higher incidence of fetal mortality in all nickel-fed groups in the F_{1a} generation and at 500 and 1000 ppm in the F_{1b} generation. No such effect in the F_2 or F_3 generation. Weanling body weight reduced at 1000 pm (all generations).	Ambrose et al., 1976

TABLE VIII-2 (cont.)

Duration	Species/ Strain	Sex/No.	Vehicle	Compound	Dose	Converted[a] Dose (mg Ni/kg bw)	Effects	Reference
3 generation	rats/Long-Evans BLU(LE)	5 pair/NR	drinking water	unspecified salt	0, 5 ppm Ni	0.01, 0.43[c]	Neonatal mortality was significantly increased over controls in all three generations, number of runts significantly increased in first and third generations.	Schroeder and Mitchener, 1971

[a]See text for conversion factors

[b]Includes estimated dietary intake of nickel (0.44 µg/g diet).

[c]Includes estimated dietary intake of nickel (0.31 µg/g diet).

NR = Not reported

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affected. Cytochrome oxidase activity exhibited a dose-related decrease in both the heart and liver but this depression was significant ($p<0.005$) only in the hearts of the high dose group. Iron concentration was significantly ($p<0.05$) increased in red blood cells and in all organs tested (heart, kidney, liver and testes) in the 1000 ppm group. Elevated organ concentrations of iron were also observed at 500 ppm (50 mg Ni/kg bw) group. No significant effects in comparison with control levels were observed at 100 ppm (10 mg Ni/kg bw) on body weight, mineral content and enzyme activity. The 100 ppm (10 mg Ni/kg bw) dose is considered a NOAEL while 500 ppm (50 mg Ni/kg bw) is a LOAEL.

Lestrovoi et al. (1974) found significantly decreased thyroid absorption of iodine when nickel (as nickel chloride) was administered orally to rats at doses of 0.5-5.0 mg/kg/day for 2-4 weeks. This study was reported in an abstract with insufficient experimental detail to evaluate the results.

In a study designed to evaluate the effects of nickel on carbohydrate metabolism, Clary (1975) added 225 ppm of nickel (as nickel chloride) to drinking water of rats (male albino, 180 g, 10/group). Assuming that the average daily water consumption of rats is equivalent to 7.8% of their body weight, the daily dose of 225 ppm is ~17.6 mg Ni/kg bw. After 4 months of exposure, rats were sacrificed and body weight was significantly ($p<0.05$) reduced compared with controls. Daily urinary volume was significantly ($p<0.05$) reduced, as was urinary zinc and calcium. Daily water consumption was not reported. Urinary sodium, potassium and glucose (after glucose loading 4 hours before sacrifice) were not significantly affected. At

sacrifice, serum lipid and cholesterol concentrations were significantly ($p<0.05$) reduced. Since only one dose level was evaluated, no dose-response relationship was established and an estimate of a NOAEL cannot be made.

Several additional subchronic toxicity studies of nickel in laboratory animals (Ashrof and Sybers, 1974; Weber and Reid, 1969; von Waltschewa et al., 1972) were available only as abstracts or as reviewed by NIOSH (1977). The results of these studies will be briefly summarized but the experimental designs and results are not reported in sufficient detail to use these studies for risk assessment.

Ashrof and Sybers (1974) fed rats diets containing nickel acetate at concentrations of 0.1%-1.0% (usually increasing to 1.0%) for 10-190 days. High mortality was observed along with other toxic signs including hypoplasia of bone marrow, thymus and spleen, progressive renal tubular degeneration, mural exudative pulmonary alveolar lesions and noninflammatory lysis of pancreatic exocrine cells. Assuming the daily dietary consumption of rats is equivalent to 5% of their body weight, doses of 0.1-10% nickel acetate are equivalent to daily doses of nickel increasing from 16.6-166 mg Ni/kg bw. This dose range may be conservative because the investigators reported that food consumption was double normal consumption. The highest daily dose is considerably higher than the oral LD_{50} values for nickel administered as nickel acetate.

Weber and Reid (1969) found that nickel added to the diets of mice resulted in reduced body weight gain in females at a dietary concentration of 1100 ppm nickel and reduced body weight gain in both males and females at

1600 ppm. Liver and heart cytochrome oxidase, liver isocitric dehydrogenase and kidney and heart malic dehydrogenase activities were reduced. The abstract did not indicate at which dietary levels these reductions were observed or the duration of the study.

The testicular effects of subchronic oral exposure of rats to nickel sulfate was examined by von Waltschewa et al. (1972). Daily doses of nickel sulfate were administered by oral intubation to 5-month-old male rats at 25 mg/kg bw for 120 days. Histopathological examination revealed degenerative cellular changes in the liver and kidney. Testes were smaller in the treated rats than in controls. Additional testicular changes in treated rats included interstitial cell proliferation, transparent vessel walls, reduced number of spermatozoa and their precursors and decreased concentrations of succinodehydrogenase and steroid 3-B-dehydrogenase. No statistical results were reported in the review by NIOSH (1977). Adverse testicular effects have also been reported following s.c. or i.p. injection of nickel sulfate (Mathur et al., 1977; Hoey, 1966).

Long-Term Exposure. In a 2-year feeding study using Beagle dogs, Ambrose et al. (1976) fed nickel sulfate hexahydrate to dogs (3/sex/group) at dietary levels of 0, 100, 1000 or 2500 ppm nickel. Assuming that dog food consumption is equivalent to 2.9% of their bw/day, these exposure levels are ~0, 3, 29 and 70 mg Ni/kg bw, respectively. The dogs on the 2500 ppm (70 mg Ni/kg bw) diet vomited after eating for the first 3 days of the experiment, so this dose was reduced to 0 then increased incrementally to 2500 ppm over a period of ~2 months. No further signs of GI irritation were observed. No significant effects on body weight, hematology, urinalysis,

organ-to-body weight ratios or histopathology were noted at 100 or 1000 ppm (3 and 29 mg Ni/kg bw, respectively). At the high dose (2500 ppm), food consumption was similar, but body weight gain was depressed, hematocrit and hemoglobin values tended to be lower (no statistical analysis was reported) and kidney-to-body weight and liver-to-body weight ratios were significantly ($p<0.05$) higher. Pathological changes in the lungs included multiple subpleural peripheral cholesterol granulomae, focal cholesterol pneumonia, bronchiolectasis and emphysema. Granulocytic hyperplasia of the bone marrow was also observed. Based on these findings, the 1000 ppm (29 mg Ni/kg bw) group represents the NOAEL and the 2500 ppm (70 mg Ni/kg bw) group represents the LOAEL for these effects.

Ambrose et al. (1976) also reported the results of a 2-year feeding study in rats given 0, 100, 1000 or 2500 ppm nickel (as nickel sulfate hexahydrate) in the diet. Assuming the daily food intake of rats is equivalent to 5% of their body weight, these daily doses are ~0, 5, 50 and 125 mg Ni/kg bw. No significant effects were reported at 100 ppm nickel (5 mg Ni/kg bw). Body weight was significantly ($p<0.05$) decreased at all measurement times (1, 3, 6, 13, 26, 52, 78 and 104 weeks) in both male and female rats fed 2500 ppm nickel (125 mg Ni/kg bw) compared with controls. Body weight was also reduced at 1000 ppm (50 mg Ni/kg bw); this reduction was significant ($p<0.05$) for females at 6 weeks and at >26 weeks. In males, body weight was reduced in the 1000 ppm group significantly ($p<0.05$) only at the 52-week determination. The investigators indicated that the decreased body weight may be due in part to decreased food consumption. Groups of female rats on the 1000 or 2500 ppm nickel diets (50 and 125 mg Ni/kg bw, respectively) had significantly ($p<0.05$) higher heart-to-body weight ratios and

significantly lower liver-to-body weight ratios than controls. The dose of 1000 ppm (50 mg Ni/kg bw) represents a LOAEL from this study, while the 100 ppm (5 Ni/kg bw) dose is a NOAEL.

Schroeder et al. (1974) added 5 ppm nickel to the drinking water of rats for life. The diet of both experimental and control groups contained 0.44 µg Ni/g diet. Average daily doses estimated from food and water consumption data are 2.6 and 37.6 µg Ni/adult rat for the control and experimental rats, respectively. Body weights tended to be somewhat higher in the male and female nickel groups than in the controls for the first year. These differences were significant at some measurement times, although at 360 days the body weights of males (400 g) and females (258 g) were nearly identical to controls. At 18 months mean body weight of both male and female nickel groups was significantly ($p<0.025$) less than controls. Lifespan was not affected. Histopathology at death revealed no differences between groups except for an increased ($p<0.025$) incidence of focal myocardial fibrosis (13.3%) in nickel groups compared with controls.

In an earlier chronic study Schroeder et al. (1964) fed mice a diet devoid of cadmium and low in other metals and added 5 ppm nickel to their drinking water. This dose is equivalent to a daily dose of 0.85 mg Ni/kg bw assuming water consumption is equivalent to 17% of their bw/day. Early mortality was observed in male mice of both control and nickel group, which the investigators suggested may be due to a deficiency in the diet. There was no significant difference on longevity between control and nickel groups. The body weight of animals dying after 1 year was depressed 4-13%

over controls. No clear adverse effects were observed in these two chronic studies at levels of 0.41 mg Ni/kg bw in rats (Schroeder et al., 1974) and 0.85 mg Ni/kg bw in mice (Schroeder et al., 1964).

The toxicity of dietary nickel has been studied in chicks (Ling and Leach, 1979; Weber and Reid, 1968) and calves (O'Dell et al., 1970). Adverse effects were seen at dietary levels ranging from 250-700 mg Ni/kg diet. These studies are of limited use for quantification of adverse effects in humans because the species (calves or chicks) are not good models for humans.

Transplacental transfer of nickel is well documented in laboratory animals (Jacobsen et al., 1978; Sunderman et al., 1978a,b; Lu et al., 1976, 1979; Olsen and Jonsen, 1979; Phatak and Patwardhan, 1950). Effects on reproduction of dietary nickel were assessed in a 3-generation study using albino, Wistar-derived rats (Ambrose et al., 1976). Nickel sulfate hexahydrate was fed to 4-week-old male and female rats (57-60 g) in chow at levels of 0, 250, 500 or 1000 ppm nickel. Assuming that the average daily food consumption of rats is equivalent to 5% of their bw, the dose levels are ~12.5, 25 and 50 mg Ni/kg bw. After 11 weeks of feeding, 20 females were mated with males from the same dietary group. About 10 days after the F_{1a} generation was weaned the parents were remated to produce the F_{1b} generation. A similar protocol was followed for the production of the subsequent generations. The number of females mated/group ranged from 17-20.

The adult body weight was slightly decreased over controls at mating and weaning in the 1000 ppm (50 mg Ni/kg bw) group. Fertility, gestation,

viability and lactation indices were not affected. The body weights of weanlings from rats on the 1000 ppm (50 mg Ni/kg bw) diet was reduced in all generations. Gross observation of weanlings of all generations and histopathology of F_{3b} weanlings (10/sex/group) provided no evidence of teratogenicity. The incidence of stillborn pups in the 250, 500 and 1000 ppm groups (12.5, 25 and 50 mg Ni/kg bw, respectively) was 17/89 (19%), 13/109 (12%), 16/109 (15%), respectively, in the F_{1a} generation and 6/170 (4%), 27/136 (20%) and 31/124 (25%), respectively, in the F_{1b} generation compared with 5/118 (4%) and 3/146 (2%) in the control F_{1a} and F_{1b} generations. No statistical analysis of the data was reported. Elevated incidences of fetal mortality were not observed in the F_2 or F_3 generations except for the F_{2b} generation at 250 ppm (12.5 mg Ni/kg bw) in which 16/197 (8%) of the pups were stillborn compared with 1/50 stillborn pups in the control group.

This study (Ambrose et al., 1976) has several design limitations including small sample size (17-20 females mated/generation) and use of pups rather than litters as the unit for comparison (the incidence of stillborn pups can be markedly elevated by a single stillborn litter). Furthermore, the results are equivocal and do not clearly define a NOAEL or LOAEL. The incidence of stillborn pups did not exhibit a consistent dose-response relationship, the incidence of stillborn pups in the 250 ppm (12.5 mg Ni/kg bw) groups was increased in the F_{1a} but not the F_{1b} generation and the elevated incidences of stillborn pups observed in the first generation did not occur in the subsequent two generations.

In another 3-generation study five pairs of weanling Long Evans BLU:(LE) rats were provided drinking water containing 5 mg Ni/ℓ nickel (as an unspecified soluble salt) (Schroeder and Mitchener, 1971). The food contained 0.31 ppm nickel. Conversion of the dose to mg/kg bw must include a number of assumptions on animal weight, food consumption and water consumption not provided by the authors. All such assumptions are based upon the lower range estimates for mature rats reported by Arrington (1972). Using the lower range for mature rats is believed to partially account for the high variability in body weight and food and drinking water consumption associated with the exposure of rats from birth through mating. For drinking water, rats weighing an average of 0.3 kg and consuming 0.025 ℓ water/day were assumed to derive an estimated daily dose of 0.417 mg Ni/kg bw (5.0 mg Ni/ℓ water x 0.25 ℓ water/0.3 kg bw). For the additional dose from food, the rats were assumed to consume 0.012 kg food/day to derive an estimated daily dose of 0.012 mg Ni/kg bw (0.31 mg Ni/kg diet x 0.012 kg diet/0.3 kg bw). Thus, a total daily dose of 0.429 mg Ni/kg bw (rounded to 0.43) is estimated from both drinking water and food. The control animals received an estimated dose of 0.01 mg Ni/kg bw from the food alone.

The concentrations of trace metals in the drinking water and food were restricted and exposure to trace metals in the environment was minimized. This diet was found to be deficient in trace metals (particularly chromium). Because of the interactions of nickel with other trace metals, the restricted exposure to trace metals may have contributed to the toxicity of nickel.

The five pairs of rats were allowed to breed freely up to ~9 months of age. Pairs of weanlings were randomly selected from the F_1 generations to produce the F_2 generations, which were similarly selected to produce the F_3 generation. Neonatal mortality was significantly ($p<0.025$) increased in all generations of exposed rats compared with controls. The number of runts was reportedly significantly ($p<0.025$) increased in the first and third ($p<0.0001$) generations. Average litter size was somewhat reduced in the F_3 generation (8.1 in exposed compared with 11.0 in controls), but the statistical significance of this difference was not reported.

The ambient water criteria was originally based on this study (U.S. EPA, 1980) but the criterion was subsequently revised because a number of design problems precluded the use of the Schroeder and Mitchener (1971) study for risk assessment purposes (U.S. EPA, 1982). Design problems included small sample size (five females were mated to produce the F_1 generation), use of diets low in trace metals (deficient in chromium) and use of animals rather than litters as the unit for statistical analysis. An attempt was made to duplicate these results, however, the investigators were unsuccessful.

Phatak and Patwardhan (1950) found no significant differences in the litter size and initial body weight of pups when male and female rats were fed diets containing 250, 500 or 1000 ppm nickel [daily dose of 10, 20 or 40 mg Ni/kg bw, respectively, assuming the rats weighed 0.3 kg and consumed 0.012 kg food/day (Arrington, 1972)]. The dietary exposure to nickel began 8 weeks before breeding and continued through lactation.

Rigaut (1983), summarizing a study by Nadeenko et al. (1979), reported that pregnant rats were administered nickel chloride in drinking water for an unspecified number of days. No effects were observed at a dose level of 0.5 μg Ni/kg, but the number of implanted embryos was decreased at 5 μg Ni/kg and surviving fetuses were smaller than controls at 500 μg Ni/kg. The review does not provide sufficient experimental details to permit evaluation of these results.

Nickel chloride has been tested for teratogenicity and fetotoxicity in rats and mice by i.p. or i.m. injection (Chernoff and Kavlock, 1982; Lu et al., 1979; Sunderman et al, 1978b).

No clinical or epidemiological studies dealing with oral exposure of humans to excessive levels of nickel were found in the available literature. Occupational exposure to nickel occurs primarily by inhalation and dermal routes and is not directly relevant to this evaluation.

Quantification of Noncarcinogenic Effects

1-Day Health Advisory. Insufficient data preclude the derivation of a 1-day HA for nickel. The available short-term (1-15 days) toxicity studies of nickel using the oral route of exposure reported only frank effects (LD_{50}s). The toxicokinetic data for nickel do not support a route-to-route extrapolation from either inhalation or parenteral routes of exposure.

10-Day Health Advisory. Dose-response relationships were observed in the 6-week dietary study by Whanger (1973), defining a NOAEL for nickel of

100 ppm diet (10 mg Ni/kg bw) and a LOAEL of 500 ppm diet (50 mg Ni/kg bw). The biological endpoints included body weight gain, hematology parameters and cytochrome oxidase activity. No other oral studies of 30- to 90-day duration were reported in sufficient detail for use in risk assessment.

The 10-day HA for a 10-kg child is calculated as follows:

$$\frac{(10 \text{ mg Ni/kg bw/day})\ (10 \text{ kg})}{(1 \text{ ℓ/day})\ (100)} = 1.0 \text{ mg Ni/ℓ}$$

where:

10 mg Ni/kg bw/day = NOAEL for effects on weight, hematology parameters and cytochrome oxidase activity in rats following 6-week oral exposure (Whanger, 1973)

10 kg = assumed body weight of child

1 ℓ/day = assumed water consumption by 10-kg child

100 = uncertainty factor.

This uncertainty factor was selected based upon the NAS/ODW guidelines in which a NOAEL from an animal study is used.

The 10-day HA for a 70-kg adult is calculated as follows:

$$\frac{(10 \text{ mg Ni/kg bw/day})\ (70 \text{ kg})}{(2 \text{ ℓ/day})\ (100)} = 3.5 \text{ mg Ni/ℓ}$$

where:

10 mg Ni/kg bw/day = NOAEL for effects on weight, hematology parameters and cytochrome oxidase activity in rats following 6-week oral exposure (Whanger, 1973)

70 kg = assumed body weight of adult

2 ℓ/day = assumed water consumption by 70-kg adult

100 = uncertainty factor.

This uncertainty factor was selected based upon the NAS/ODW guidelines in which a NOAEL from an animal study is used.

Lifetime Adjusted Acceptable Daily Intake (AADI). There is no one study entirely suitable for use in estimating an AADI for nickel. The candidate studies for this calculation are the studies in rats by Ambrose et al. (1976) in which large amounts of nickel were administered in feed and the study in rats by Schroeder and Mitchener (1971) in which small amounts of nickel were administered in water. Both studies (as reported) have significant scientific limitations that must be considered. The major weakness with the Schroeder and Mitchener (1971) study is that the end result is based on a total of five matings. The matings were not randomized and the males were not rotated. Additional statistical analyses are also needed. Unfortunately, because of the small number of animals used, little confidence can be placed in the results.

Some of the results of Ambrose et al. (1976) are questionable because of the statistical analysis of the data. For example, in the reproductive study the effect of litter on the outcome was not considered. Thus, one must assume that the deaths among littermates are independent. If this assumption is not met (and it should not be due to genetic similarities), the statistically positive results are highly questionable. These statistical problems are clearly summarized by Seilkop (1982). Following a thorough statistical review of all the information reported by Ambrose et al. (1976), the only effect seen was a lower mean body weight in the 1000 ppm dietary dose group compared with the controls in the 2-year feeding study in rats.

Unsuccessful attempts were made to obtain the original data for reanalysis. Thus, the only data from this study useful for risk estimation are those data that demonstrate a lower mean body weight in one exposure group. However, the route of administration used must be considered. A recent investigation by Foulkes (1984) demonstrated that food (i.e., milk) reversibly inhibits the removal of nickel from the jejunal lumen. The author concludes that food can exert a major influence on nickel absorption but that it is not known if food constituents in chow or other diets would inhibit nickel absorption as much as milk. Nevertheless, the use of diet-based nickel toxicity studies for the estimation of a drinking water criterion may have only limited relevance.

Therefore, using the data of Ambrose et al. (1976), the lower mean body weight detected in the 1000 ppm dietary dose group is regarded as an adverse effect. This effect was not seen in the 100 ppm dietary dose group. Thus, 100 ppm in the diet can be used to determine a NOAEL and the ADI is estimated as follows:

$$ADI = \frac{[(100\ ppm)\ (0.05)\ (70\ kg)]\ (0.2)}{(100)}$$

where:

1) the dietary dose (ppm) is converted to a mg/kg dose by assuming that an adult rat consumes 5% of its body weight as food.

2) 70 kg is the body weight of a human adult.

3) 0.2 represents an assumed difference in absorption of nickel in water vs. milk.

4) the uncertainty factor of 100 is used, since these are good chronic toxicity animal data identifying a NOAEL.

thus,

$$ADI = \frac{[(5\ mg/kg/day)\ (70\ kg)]\ (0.2)}{100}$$

$$= 0.7\ mg/day \text{ or } 700\ \mu g/day$$

If all the daily intake is apportioned to water, the AADI is estimated as follows:

$$AADI = \frac{ADI}{2\ \ell/day}$$

where:

2 ℓ/day is the assumed drinking water consumption by a 70 kg adult

thus,

$$AADI = \frac{700\ \mu g/day}{2\ \ell/day}$$

$$= 350\ \mu g/\ell$$

This AADI calculation assumes 100% of the human exposure derives from drinking water. This value may be modified upon the availability of relative source contribution data which provide estimates of human exposure from food, air and possibly the occupational environment.

Carcinogenic Effects

A number of reviews have discussed the carcinogenicity of nickel compounds (U.S. EPA, 1980; NIOSH, 1977; IARC, 1976; NAS, 1975; Sunderman, 1981, 1979, 1977a, 1976, 1973). It is apparent from these reviews that the chemical form and route of exposure are important factors in determining the carcinogenic potential of nickel. The soluble nickel salts do not generally

appear to be carcinogenic, although repeated i.p. injections of nickel acetate at a dose of 360 mg/kg induced lung carcinomas in mice (Stoner et al., 1976).

The results of several oral studies suggest that 5 ppm nickel in drinking water is not carcinogenic to rats and mice (Schroeder et al., 1974; 1964; Schroeder and Mitchener, 1975). Schroeder et al. (1974) exposed a group of 52 male and 52 female weanling Long-Evans rats to 0 or 5 ppm nickel in drinking water for life. The diet for both control and treated groups contained an estimated 0.44 μg Ni/g of food. Assuming the average daily food and water consumption of the rats was ~5% and 7.8% bw, respectively, average daily doses can be calculated as 0.02 and 0.41 mg Ni/kg bw for control and exposed rats, respectively. Tumor incidences were determined after natural death of the experimental animals. Longevity of control and exposed rats was similar. There were no significant differences in tumor incidences (sarcomas, lymphomas or carcinomas) between the exposed and control groups.

In an earlier study with mice, Schroeder et al. (1964) exposed 50 male and 54 female Charles River mice to 5 ppm nickel in drinking water. This is a daily dose of ~0.85 mg Ni/kg bw assuming mice consume water at a rate equivalent to 17% of their bw/day. No estimate of dietary nickel intake was provided, although the investigators stated that it was low. Causes of death were determined at autopsy in 33 and 41 treated females and males, respectively, and 60 female and 44 male controls. The number of deaths from all tumor types was significantly ($p<0.01$) lower in treated females compared with controls. No other statistically significant differences in causes of death or longevity were observed. Early mortality was observed in both the exposed and control groups.

Schroeder and Mitchener (1975) indicated that the mice in the Schroeder et al. (1964) study above were chromium-deficient, so the study was repeated using a diet containing adequate chromium. Charles River-CD Swiss mice (54/sex/group) were given 5 ppm nickel (as nickel acetate) in drinking water for life. The lifespan of females was significantly longer in the nickel-fed mice than in the controls; there was no significant difference in males. Tumor incidences did not differ significantly between the nickel-fed groups and the controls.

The carcinogenic potential of nickel ingested by laboratory animals at doses higher than 5 ppm in drinking water cannot be evaluated from the available literature. Available human clinical and epidemiological carcinogenicity studies are limited to inhalation exposure.

The findings of animal carcinogenicity studies using inhalation or parenteral routes of exposure are summarized as follows. Metallic nickel, nickel subsulfide (Ni_3S_2) and nickel carbonyl ($Ni(CO)_4$), which are insoluble nickel compounds, have been shown to induce tumors in a number of laboratory animals primarily at the site of exposure (Heath and Webb, 1967; Heath and Daniel, 1964; Mitchell et al., 1960; Hueper, 1955, 1958; Gilman, 1962; Jasmin and Riopelle, 1976; Damjanov et al., 1978; Ottolenghi et al., 1974; Sunderman et al., 1959, 1980; Sunderman and Donnelly, 1965). Intravenous injection of nickel carbonyl resulted in liver and kidney sarcomas (Lau et al., 1972).

In humans it has been demonstrated that the incidence of respiratory tract cancers in nickel refinery workers is statistically significantly

elevated (NIOSH, 1977; IARC, 1976; NAS, 1975). The inhaled compound or compounds responsible for the elevated incidence of cancer have not been identified but candidates include nickel carbonyl, nickel subsulfide, nickel oxide and metallic nickel particulates (Sunderman, 1977a,b). In addition to lung and nasal cavity tumors several other cancer risk categories (laryngeal, gastric and soft tissue cancers) have been suggested based on occupational studies (Pedersen et al., 1973; Saknyn and Shabynina, 1973; Sunderman, 1976) but none of these have been widely demonstrated. Since inhalation exposure to nickel compounds is not a relevant route of exposure for assessing the carcinogenic potential of nickel in drinking water, the epidemiological studies will not be discussed here.

A number of studies conducted to help elucidate the mechanisms of nickel carcinogenesis are reviewed by Sunderman (1976) and Leonard et al. (1981). Binding of nickel to RNA/DNA and inhibition of RNA or DNA synthesis by nickel compounds has been demonstrated (Beach and Sunderman, 1970; Heath and Webb, 1967; Witschi, 1972; Basrur and Gilman, 1967). Nickel has induced DNA strand breaks and DNA repair activity in hamster cells in vitro (Robinson and Costa, 1982; Robinson et al., 1983, 1982). Lee et al. (1982) and Ciccarelli et al. (1981) have reported formation of protein-nickel-DNA complexes in mammalian systems.

Nickel chloride was negative for mutagenicity in Escherichia coli (Green et al., 1976) and Bacillis subtilis (Kanematsu et al., 1980; Nishioka, 1975). However, nickel chloride and nickel sulfate have been shown to be mutagenic or weakly mutagenic in eukaryotic test systems (Miyaki et al., 1979; Amacher and Paillet, 1980; Wulf, 1980).

Results of animal studies suggest that nickel acts in a synergistic manner with polycyclic aromatic hydrocarbons (20-methylcholanthrene and benzopyrene) for the induction of malignant tumors (Toda, 1962; Maenza et al., 1971; Kasprzak, et al., 1973). Synergism of nickel and Newcastle Disease virus has been suggested by the in vitro supression of mouse L-cell interferon synthesis in the presence of the virus and nickel (Treagan and Furst, 1970).

Quantification of Carcinogenic Effects

Nickel was negative for carcinogenicity when tested at low concentrations (5 ppm) in drinking water in both rats and mice (Schroeder et al., 1974, 1964; Schroeder and Mitchener, 1975) but no oral carcinogenicity bioassays using higher nickel concentrations are available, even though dietary nickel remains the largest source of nickel exposure to humans. Thus, there is no current evidence to suggest that a carcinogenic response is induced in humans or laboratory animals by the ingestion of nickel compounds. Several nickel compounds (metallic nickel, nickel subsulfide and nickel carbonyl) have a carcinogenic potential when exposure occurs by inhalation or parenteral routes. The resultant tumors tend to be site-specific.

The IARC has performed an assessment of the degree of evidence for the carcinogenicity of nickel to humans and in experimental animals (WHO, 1982). This assessment concluded that nickel and certain nickel compounds are group 2A chemicals (a relatively high degree of evidence exists to demonstrate that the chemical is probably carcinogenic to humans). This IARC classification is based upon an evaluation of the carcinogenic potential of nickel from inhalation and intramuscular injection. As stated

earlier, at present there is insufficient evidence to classify nickel as a carcinogen following oral exposure.

Existing Guidelines and Standards

U.S. EPA (1980, 1982) derived an ADI of 1.46 mg Ni/day with an ambient water quality criterion of 0.632 mg Ni/ℓ. This derivation was based on the 3-generation reproductive study by Ambrose et al. (1976), considering 250 ppm dietary nickel to be a LOAEL because of an increased incidence of stillborn pups in the F_{1a} generations. The discussion in the AADI Section indicates why this study was not considered appropriate for derivation of an AADI. The AADI values of 1.8 mg Ni/ℓ and 0.15 mg Ni/ℓ calculated herein bracket the ambient water quality criterion (0.632 mg Ni/ℓ).

For occupational exposure the ACGIH (1983) has established a TWA-TLV of 1.0 mg Ni/M³ for metallic nickel and 0.1 mg Ni/M³ for soluble nickel salts. The NIOSH (1977) criterion for occupational exposure to nickel is a TWA of 15 μg Ni/m³.

Special Considerations

High Risk Populations. Nickel allergy resulting in contact dermatitis and other dermatalogic effects has been discussed in detail in a number of reviews (Rigaut, 1983; U.S. EPA, 1980; NAS, 1975). The incidence of nickel allergy in the general United States population is not well documented. The North American Contact Dermatitis Group (1973) studied 1200 subjects who were patients of dermatologists in 10 North American cities. Using a standardized patch test, 11% of the individuals exhibited positive responses to nickel. A study of 4825 Europeans conducted by the International Contact

Dermatitis Group reported an overall incidence of positive reactions to nickel of 6.7% (Fregert et al., 1969). Two studies not restricted to dermatology patients reported reaction rates of 4.5% in Finland and 5.8% in San Francisco (Peltonen, 1979; Prystowsky et al., 1979). There was a much higher incidence of nickel sensitivity in females than males in all four studies cited above. For example, 9% of the women and only 0.9% of the men exhibited positive reactions to nickel in the San Francisco study (Prystowsky et al., 1979). It is not clear whether nickel sensitivity is due to a particular physiological condition. Nevertheless, individuals with positive reactions to patch tests for nickel can be considered to be a special group at increased risk.

Of particular significance with regard to the evaluation of nickel in drinking water are the findings that chronic dermal nickel allergy in humans is affected by oral intake of nickel. Kaaber et al. (1978) found that ingestion of 2.5 mg nickel (as nickel sulfate) aggravated nickel dermatitis in 17/28 patients, while 6 weeks on a low nickel diet resulted in improved conditions in 9/17 patients. These results are in agreement with other studies. Jordan and King (1979) observed improvement in dermatitis with reduced daily nickel ingestion; Christensen and Moller (1975) found that ingestion of 5.6 mg nickel aggravated hand eczema; and Cronin et al. (1982) reported that dermatitis was aggravated in 8/10 subjects ingesting 0.62 mg Ni/day for 4 days but a single dose of 0.62 mg Ni had no effect. These results suggest that individuals with nickel allergy may have increased sensitivity to ingestion of nickel in drinking water.

McConnell et al. (1973) reported a case of asthma that developed in a 24-year-old male within several weeks of beginning work in a nickel metal-plating company. Controlled inhalation exposures of the subject to a nickel sulfate aerosol resulted in respiratory distress. This effect was not observed in a volunteer serving as a control. Several other recently reported cases of asthma associated with inhalation exposure to nickel are cited by Rigaut (1983).

Pregnant women are a potential special risk group. Transplacental transfer of nickel has been well documented in rats and mice (Phatak and Patwardhan, 1950; Lu et al., 1976; Jacobsen et al., 1978; Olsen and Jonsen, 1979; Sunderman et al., 1978a). Transplacental movement of nickel has also been indicated in humans. Casey and Robinson (1978) found levels of nickel in liver, heart and muscle of fetuses that were comparable to levels in adults. There is no evidence of adverse effects to the human fetus that is due to nickel, but fetotoxic effects have been observed in rats and mice administered nickel by oral or parenteral routes (Ambrose et al., 1976; Lu et al., 1979; Sunderman et al., 1978a).

Certain subpopulations are at increased risk to the effects of nickel because of higher inhalation or dermal exposures to nickel than those experienced by the general population. Occupational exposure to nickel occurs in industries such as nickel mining and refining, electroplating and other metal alloy work. Dermal exposure to nickel from stainless steel kitchens, cooking utensils, household chemicals and jewelry may place some persons at special risk to nickel dermatitis. Nickel is present in some hairdressing preparations. Therefore, hairdressers may also be at special risk to nickel

dermatitis. Inhalation exposure to nickel is increased by cigarette smoking. NAS (1975) estimated a daily inhalation of 3-15 μg nickel for individuals smoking two packs of cigarettes/day.

Interactions. Interactions of nickel with other compounds will be only briefly summarized here. There is apparently a nutritional interaction between nickel and iron in laboratory animals. Nickel deficiency in rats resulted in anemia that was due to reduced intestinal absorption of iron (Schnegg and Kirchgessner, 1976a,b). Reduced hemoglobin and hematocrit values in irondeficient rats were offset by nickel supplementation when dietary iron was ferric sulfate, but not when dietary iron was a mixture of ferric and ferrous sulfates (Nielsen, 1980a). Absorption of nickel from the GI tract was enhanced in iron-deficient rats (Ragan, 1978). Interactions of nickel with copper have been reported (Nielsen, 1980b) and zinc metabolism was adversely affected by nickel deficiency (Anke et al., 1980).

Effects in rats of oral exposure to nickel, such as reduced growth rate and alterations of hepatic and renal enzyme activities, were offset by co-administration of high doses of vitamin C (Chatterjee et al., 1980). Prasad et al. (1980) found that divalent nickel antagonized digoxin-induced cardiac arrhythmias in rats, rabbits and guinea pigs.

Nickel is present in asbestos but its role, if any, in the carcinogenicity of asbestos is unclear. As reported in the Carcinogenic Effects Section, the induction of malignant tumors by several polycyclic aromatic hydrocarbons was enhanced by nickel (Toda, 1962; Maenza et al., 1971;

Kasprzak et al., 1973). In addition, one of these compounds, benzo(a)-pyrene, exhibited a comutagenic effect with nickel sulfate in hamster embryo cells (Rivedal and Sanner, 1980, 1981).

Beneficial Effects. According to a review by Nielson (1982), signs of nickel deficiency have been reported for rats, minipigs, cows, goats, sheep and chickens. In a 3-generation study using rats (Nielsen et al., 1975), the nickel-deficient group was characterized by higher perinatal mortality, reduced average body weights of pups, decreased hematocrits, pale livers, decreased liver cholesterol, decreased quantity and organization of rough endoplasmic reticulum, higher total lipids and lower phospholipids in the liver compared with controls. These differences were significant ($p<0.05$) at some, but not all, measurement times.

Schnegg and Kirchgessner (1978) observed a number of signs of nickel deprivation including significantly depressed growth, hematocrits, hemoglobin levels, erythrocyte counts, serum urea, ATP and glucose levels, hepatic triglycerides, glucose and glycogen and tissue levels of iron, copper and zinc in 30-day-old offspring from nickel-deprived rats. Nickel deficiency in chicks was characterized by altered liver metabolism and morphology (Nielsen and Ollerich, 1974; Sunderman et al., 1972; Nielsen and Higgs, 1971) and scaly dermatitis of the legs and swollen hock joints (Nielsen and Higgs, 1971).

Schnegg and Kirchgessner (1976a,b) found that nickel deficiency depressed the intestinal absorption of iron resulting in reduced tissue levels of iron and consequent anemia. The metabolic function of nickel has not

been clearly defined; Nielsen (1982) presented several possible mechanisms including functioning as a structural component or co-factor in certain metalloproteins or metalloenzymes or facilitating the intestinal absorption of the Fe^3 ion by serving as a biological cofactor.

As briefly summarized, the existence of nickel-deficiency syndrome, which is an important criterion for determining essential elements, has been demonstrated for various animal models. Although there is no definitive evidence in humans, these results are suggestive of an essential role for nickel in humans. This possible essentiality must be considered when quantifying health risks to humans from excessive exposure to nickel. Nielsen (1982) estimated that the nickel requirement in rats is ~50 µg/kg diet based on the studies by Nielsen et al. (1975) and Schnegg and Kirchgessner (1978).

Summary

The recommended values for the 10-day HAs for both adults and children, and the AADI are summarized in Table VIII-3.

TABLE VIII-3

Summary of Quantification of Toxicological Effects

	Nickel Drinking Water Concentration, (mg/ℓ)		Reference[a]
	10-kg Child	70-kg Adult	
1-Day HA	_[b]	_[b]	
10-Day HA	1.0	3.5	Whanger, 1973
AADI	_[c]	0.35	Ambrose et al., 1976

[a]Reference for NOAEL (LOAEL) used in calculating HA or AADI values.

[b]Not calculated because of insufficient data following a single oral dose.

[c]Not calculated because the child will not remain in the high risk population for a lifetime.

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